Reporting of Adverse Events to Institutional Review Boards; Public Hearing

Comments from Western Institutional Review Board (WIRB)
Presented by Owen G. Reese, Jr., MD, Executive Director

The Western Institutional Review Board would like to thank Commissioner Crawford and the FDA for the opportunity to address this very important, yet frustrating issue. Our experience corroborates the FDA's impression that the process is burdensome and does not provide the information necessary for us to fulfill our mission of subject protection.

WIRB has extensive experience in the review of adverse event reports. In 2004, we received and reviewed approximately 12,000 site-generated adverse event reports. WIRB also received and reviewed over 14,000 new sponsor generated reports, such as IND safety reports. The effort required to process and review this volume of material is daunting. We dedicate 3 full-time staff members to processing the reports and entering the information into our computer system. Each report is then evaluated by one of three medically trained pre-reviewers seeking to identify all events that are likely to be unanticipated and possibly related. These then undergo physician review. Physician review now requires a full FTE for this task, and we are not convinced that this significant investment of personnel time produces subject safety gains commensurate with other IRB activities.

The process is plagued with inefficiency. In addition to the 60 new reports we receive on a daily basis, we receive 250 to 350 duplicate sponsor generated reports and of the site-generated AEs, 70% were considered by the investigator to be not-related to the study drug, device, or procedures of the study. Of course, the reports must be reviewed to discover this duplication and low relevance.

Although 21 CFR 312.32(c)(B)(ii) charges sponsors to identify in each IND safety report, all reports previously filed with the IND concerning similar adverse experiences and to analyze the significance of the adverse experience in light of previous, similar reports, very few sponsors provide this required information spontaneously. Because in multi-center trials, we usually lack the knowledge of the total number of subjects at risk, we are forced to either evaluate the significance of events in isolation or spend countless hours obtaining additional information from sponsors. In the past, when serving as the central IRB for a large study of the NSAID diclofenac (Voltaren), WIRB was able to identify gastric perforation as a significant risk prior to notification by the sponsor; such occasions are rare in today's environment.

We concur with the conclusion of the NIH Regulatory Burden: Humans Subjects Protection Workgroups report, that off-site reports:

1. Are not presented in a useful format
2. Are commonly duplicated
3. Often do not present unblinded data, and

4. In presenting data without interpretation, provide no useful information from which the IRB can take appropriate action.

For multi-site studies, reports that do suggest an increase in risk are usually accompanied by suggested consent form and, if needed, protocol revisions. In other words, the evaluation of the problem and the determination of any action needed are made without input from the IRB. In many cases it is apparent that the FDA has been involved in the process of determining the action to be taken by the sponsor. This calls into question the utility of having the IRB review these reports at all.

In recent months, well-publicized problems involving rofecoxib and natalizumab led to drastic action. From WIRB's perspective, the actions taken on these drugs were done without any input or direction from any IRB. In the case of rofecoxib, WIRB was able to identify all protocols using this drug as either the study drug or a comparator and contact investigators with a plan for notification of subjects that had been reviewed by the Board. Earlier notification would have resulted in a more coordinated and more timely approach.

Let me now address the specific questions identified in the hearing notice:

1. What role should IRBs play in the review of adverse events information and is there a difference in the role for single-site and multi-site trials?

   WIRB believes that any multi-site study that might involve significant risks to subjects should be required to constitute a DSMB to monitor adverse events <u>in real-time</u> and evaluate the impact of those events in the context of the entire study. The DSMB charter must require that significant conclusions be reached and forwarded to the involved IRBs in a timely manner. The IRB's role should not be to review the individual adverse events for these studies, but rather evaluate the DSMB findings and recommendations to determine when and how the subjects should be informed, protocols amended, or studies stopped.

   For single-site research, it is important that all adverse events are reviewed by an entity independent of the investigator in order to give an additional perspective to the relatedness and severity of an event. A sponsor will customarily provide this review, however, investigator-sponsored research is often not monitored by another entity and should have closer scrutiny. The IRB must, then, fulfill this role. IRBs should have resources and procedures in place to review <u>all adverse events</u>, in addition to those judged unanticipated and those meeting the criteria of "serious" as defined in 21 CFR 312.32(a).

2. About what types of adverse events should IRBs receive information?

   Although the definition of serious adverse drug experience at 21 CFR 312.32(a) clearly encompasses events important in a subject's decision to participate, most reports received by WIRB are confined to death, life-threatening events, inpatient

hospitalizations, significant disability or birth defects. WIRB believes that a broadened interpretation of the definition is warranted, but it is particularly important for single-site, investigator sponsored research and should include all events that significantly impact a subject's quality of life, even temporarily. These would include emergency room visits, missed work, and significant discomfort or expense, as this is information important to subjects in deciding whether to participate in a research study.

Events occurring during washout periods prior to use of a study drug or device are not uniformly reported to WIRB, yet they represent "unanticipated problems involving risks to human subjects" and are important findings for subjects. IRBs should be notified of these events.

3. What should be the approach to providing adverse events information to IRBs?

   In the case of multi-center trials, the required DSMB reports should provide analyzed and summarized information; however, the basis for any conclusions and recommendations must be evident in the report, if the IRB is expected to exercise independent judgment. Such reports should be made to the IRB on a routine scheduled basis and whenever data result in a significant recommendation with respect to the protocol, investigator's brochure or informed consent.

   WIRB does not believe that receipt of reports of aggregated data without accompanying interpretation and explanation will be of value. They will by design be untimely and will in effect require each IRB to become a DSMB without the benefit of viewing unblinded data. This approach would promote inconsistency and duplication of effort. In addition, each IRB would be obligated to acquire data trending capability, requiring a statistician and specialized computer software. While WIRB has the resources to accomplish this, many IRBs would find it unduly burdensome.

   Events occurring in single site trials must be accompanied by sufficient subject history and findings for the IRB to independently assess the relationship of the event to the study drug or device. For single site studies, reports should be reviewed in real time, in order to respond to a significant problem in a timely manner.

   All reports should be standardized and should include an interpretation of the relevance of the event for other subjects in the study. Sponsors should be responsible for reporting on multi-site trials; investigators (with the assistance of a sponsor, if present) should report on single-site trials. The reporting system should be the same for drugs and devices.

Again, thank you for the opportunity you have given us to express WIRB's opinion. We are hopeful that changes in the current system will assist IRBs to accomplish their mission of subject protection by increasing the prospect of identifying unanticipated risks to their safety and well being.